SHORT PAPER

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A novel reductive cyclisation of *o*-nitrochalcones promoted by low-valent titanium: an access to 2-arylquinolines and 5,6-dihydrobenz[c]acridines†

Daqing Shi[a,b,*], Liangce Rong[b], Juxian Wang[b], Qiya Zhuang[b], Xiangshan Wang[b], Shujiang Tu[b] and Hongwen Hu[a]

[a]*Department of Chemistry , Nanjing University, Nanjing, 210093, P. R. China*

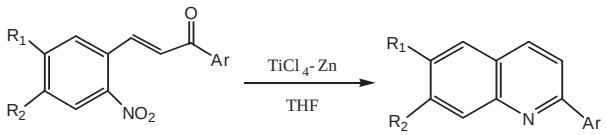
[b]*Department of Chemistry , Xuzhou Normal University, Xuzhou , 221009, P. R. China*

The intramolecular reductive cyclizations of o-nitrochalcones(**1**) induced by the $TiCl_4$/Zn system were studied; 2-arylquinolines(**2**) and 5,6-dihydrobenz[c]acridines(**4**) were obtained in reasonable yields at room temperature conditions.

Keywords: *o*-nitrochalcones, quinolines, acridines, low-valent titanium

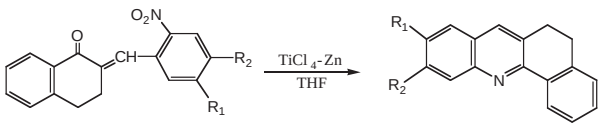
Recently there has been increased interest in the reactions induced by low-valent titanium reagents because of their use in reductive coupling of carbonyl compounds.[1] A variety of other functional groups also react.[2-5] Recently, we reported the low-valent titanium induced intermolecular reductive coupling reaction of carboxylic acid derivatives with aromatic ketones,[6] intramolecular reductive coupling reaction of 4,4-dicyano-1, 3-diaryl-1-butanone[7] and the cyclodimerisation of α,β-unsaturated ketones.[8] We now describe the reductive coupling reaction of o-nitrochalcones by treatment with titanium tetrachloride and zinc in tetrahydrofuran at room temperature.

When *o*-nitrochalcones(**1**) were treated with low-valent titanium, prepared from titanium tetrachloride and zinc powder in anhydrous THF, the intramolecular reductive coupling products(**2**) were obtained in reasonable yields.



1 **2**

Treatment of 2-(*o*-nitrobenzal)-1-tetralones (**3**) with low-valent titanium under the same reaction conditions gave the 5,6-dihydrobenz[c]acridines(**4**). These results are summarised in Table 1.



3 **4**

Quinolines have attracted interest due to their biological properties. These include quinine, primaquine, chloroquine, piperaquine, hydroxypiperaquine, chloroquine phosphate, primaquine phosphate and mefloquine which have been reported to exhibit antimalarial properties.[9-10] It has been reported that quinoline analogues have anti-inflammatory, analgesic, antihypertensive, and antidepressive properties.[11] Various methods are known for the synthesis of quinolines,[12] but most of these methods have disadvantages such as harsh reaction condition, laborious manipulation or low yield.

* To receive any correspondence. E-mail: wxs2001z@sina.com.cn

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 The reaction of *o*-nitrochalcones promoted by low-valent titanium

Entry	R^1	R^2	Ar	Yield/%[a]
2a	H	H	C_6H_5	71
2b	H	H	3-ClC_6H_4	82
2c	H	H	4-ClC_6H_4	85
2d	H	H	4-BrC_6H_4	84
2e	Cl	H	C_6H_5	82
2f	Cl	H	3-ClC_6H_4	88
2g	Cl	H	4-ClC_6H_4	90
2h	Cl	H	4-BrC_6H_4	87
4a	H	H	-	74
4b	Cl	H	-	77
4c	OCH_2	O	-	81
4d	OCH_3	OCH_3	-	93

[a]Isolated yield.

The present method has the advantage of accessible starting materials, simple and mild reaction conditions, convenient manipulation and reasonable yields. Further studies to develop other new uses of this reagent are now in progress.

Experimental

Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. All reactions were performed under a nitrogen atmosphere. Melting points were uncorrected. ^{1}H NMR spectra were obtained for solution in $CDCl_3$ with Me_4Si as internal standard using a Inova-400 spectrometer. Microanalyses were carried out using a Perkin-Elmer 2400 II analyzer. IR spectra were recorded on an FTIR-8101 spectrometer in KBr.

General procedure for the $TiCl_4$/Zn promoted reductive coupling reactions of o-nitrochalcones: $TiCl_4$ (2.2ml, 20mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (2.6g, 40mmol) in freshly distilled dry THF (20ml) at room temperature under N_2. After the completion of the addition, the mixture was refluxed for 2h. The suspension of the low-valent titanium reagent formed was cooled to room temperature and a solution of o-nitrochalcones (**1**) or (**3**) (10mmol) in anhydrous THF (10ml) was added. The mixture was stirred for 2h at room temperature under N_2. The reaction mixture was quenched with 5% HCl (100ml) and extracted with $CHCl_3$ (3 × 50ml).The combined extracts were washed with water (3 × 50ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products were purified by recrystallization from 95% ethanol to give (**2**) or (**4**).

2-phenylquinoline (**2a**): m.p. 79–81˚C (lit.[18] 83˚C) IR: 3055, 1622, 1596, 1546, 1490, 1442, 1321, 1204, 1128, 1026, 830, 792, 772, 691. ^{1}H NMR: 7.45–7.56(4H, m, ArH), 7.74(1H, t, *J*=7.2Hz, ArH), 7.84(1H, d, *J*=7.2Hz, ArH), 7.89(1H, d, *J*=8.4Hz, ArH), 8.16–8.20(3H, m, ArH), 8.24(1H, d, *J*=8.4Hz, ArH).

2-(3'-chlorophenyl)quinoline (**2b**): m.p. 59–61˚C. IR: 3034, 1621, 1596, 1548, 1474, 1329, 1190, 1100, 1079, 898, 870, 831, 811, 785, 757, 697, 670. ^{1}H NMR: 7.44–7.48(2H, m, ArH), 7.55(1H, t,

J=7.2Hz, ArH), 7.75(1H, t, *J*=7.8Hz, ArH), 7.85(2H, d, *J*=8.4Hz, ArH), 8.04(1H, d, *J*=7.2Hz, ArH), 8.17–8.24(2H, m, ArH), 8.25(1H, d, *J*=8.4Hz, ArH).Anal. Calc. for $C_{15}H_{10}ClN$:C, 75.16, H, 4.20, N, 5.84; Found: C,75.41, H, 3.94,N, 5.73%.

2-(4'-chlorophenyl)quinoline (**2c**): m.p. 112–114˚C. IR: 3043, 1623, 1588, 1552, 1486, 1430, 1127, 1090, 1008, 817, 787, 752, 714. ^{1}H NMR: 7.49–7.57(3H, m, ArH), 7.74(1H, t, *J*=7.2Hz, ArH), 7.85(2H, dd, J_1=8.4Hz, J_2=4.4Hz, ArH), 8.12–8.18(3H, m, ArH), 8.24(1H, d, *J*=8.4Hz, ArH). Anal. Calc. for $C_{15}H_{10}ClN$: C, 75.16, H, 4.20, N, 5.84; Found: C,75.23, H, 4.09, N, 5.62%.

2-(4'-bromophenyl)quinoline (**2d**): m.p. 114–116˚C. IR: 3034, 1623, 1594, 1485, 1429, 1126, 1070, 1005, 815, 787, 751, 713. ^{1}H NMR: 7.55 (1H, t, *J*=7.2Hz, ArH), 7.66(2H, d, *J*=8.4Hz, ArH), 7.77(1H t, *J*=7.2Hz, ArH), 7.85(2H, dd, J_1=8.4Hz, J_2=4.4Hz, ArH), 8.07(2H, d, *J*=7.2Hz, ArH), 8.18(1H, d, *J*=8.4Hz, ArH), 8.25(1H, d, *J*=8.4Hz, ArH). Anal. Calc. for $C_{15}H_{10}BrN$: C, 63.40, H, 3.55, N, 4.93; Found: C, 63.69, H, 3.38, N, 4.77%.

6-chloro-2-phenylquinoline (**2e**): m.p. 109–110˚C. IR: 3050, 1618, 1595, 1546, 1483, 1318, 1191, 1129, 1073, 1022, 944, 876, 833, 782,754, 715, 694. ^{1}H NMR: 7.47–7.50(1H, m, ArH), 7.54(2H, t, *J*=7.2Hz, ArH), 7.66(1H, d, *J*=8.4Hz, ArH), 7.82(1H, s, ArH), 7.91(1H, d, *J*=8.4Hz, ArH), 8.11–8.17(4H, m, ArH). Anal. Calc. for $C_{15}H_{10}ClN$: C, 75.16, H, 4.20, N, 5.84; Found: C, 75.32, H, 4.09, N, 5.92%.

6-chloro-2-(3'-chlorophenyl)quinoline (**2f**): m.p. 96–98˚C. IR: 3043, 1625, 1596, 1548, 1474, 1328, 1190, 1131, 1099, 1079, 947, 898, 870, 831, 811, 785, 757, 697, 670. ^{1}H NMR: 7.46–7.49(2H, m, ArH), 7.69(1H, d, *J*=10Hz, ArH), 7.83(1H, s, ArH), 7.88(1H, d, *J*=8.8Hz, ArH), 8.03(1H, d, *J*=5.6Hz, ArH), 8.13–8.19(3H, m, ArH). Anal. Calc. for $C_{15}H_9Cl_2N$: C, 65.72, H, 3.31, N, 5.11; Found: C, 65.83, H, 3.06, N, 4.92%.

6-chloro-2-(4'-chlorophenyl)quinoline (**2g**): m.p. 162–164˚C. IR: 3040, 1623, 1596, 1484, 1407, 1180, 1092, 1073, 1012, 886, 847, 823, 804, 665. ^{1}H NMR: 7.50(2H, d, *J*=8.88Hz, ArH), 7.67(1H, d, *J*=8.4 Hz, ArH), 7.82(1H, s, ArH), 7.87(1H, d, *J*=10Hz, ArH), 8.09–8.16(4H, m, ArH). Anal. Calc. for $C_{15}H_9Cl_2N$: C, 65.72, H, 3.31, N, 5.11; Found: C, 65.81, H, 2.94, N, 5.25%.

6-chloro-2-(4'-bromophenyl)quinoline (**2h**): m.p. 174–175˚C. IR: 3040, 1617, 1596, 1546, 1482, 1403, 1314, 1179, 1072, 886, 844, 823, 803, 657. ^{1}H NMR: 7.66–7.70(3H, m, ArH), 7.83(1H, s, ArH), 7.88(1H, d, *J*=8.8Hz, ArH), 8.06(2H, d, *J*=8.4Hz, ArH), 8.19(2H, d, *J*=8.4Hz, ArH). Anal. Calc. for $C_{15}H_9BrClN$: C, 56.55, H, 2.85, N, 4.40; Found: C, 56.71, H, 2.62, N, 4.28%.

5,6-dihydrobenz[c]acridine (**4a**): m.p. 61–63˚C. IR: 3031, 2928, 1621, 1609, 1551, 1493, 1459, 1432, 1400, 1284, 1015, 946, 912, 860, 770, 737, 615. ^{1}H NMR: 3.01(2H, t, *J*=7.2Hz, CH_2), 3.13(2H, t, *J*=7.2Hz, CH_2), 7.25–7.29(1H, m, ArH), 7.36–7.49(3H, m, ArH), 7.65(1H, t, *J*=8.4Hz, ArH), 7.75(1H, d, *J*=7.2Hz, ArH), 7.93(1H, s, ArH), 8.14(1H, d, *J*=8.4Hz, ArH), 8.58(1H, d, *J*=6.8Hz, ArH). Anal. Calc. for $C_{17}H_{13}N$: C, 88.28, H, 5.66, N, 6.06; Found: C,88.43, H, 5.48, N, 6.25%.

3-chloro-5,6-dihydrobenz[c]acridine (**4b**): m.p. 101–103˚C. IR: 3028, 2943, 1632, 1598, 1484, 1395, 1342, 1289, 1251, 1178, 1074, 1013, 914, 835, 760, 742, 725, 695, 619. ^{1}H NMR: 3.02(2H, t, *J*=6.8 Hz, CH_2), 3.13(2H, t, *J*=6.8Hz, CH_2), 7.26–7.29(1H, m, ArH), 7.37–7.45(2H, m, ArH), 7.59(1H,d, *J*=8.8Hz, ArH), 7.73(1H, s, ArH), 7.85(1H, s, ArH), 8.09(1H, s, ArH), 8.56(1H, d, *J*=4.4Hz, ArH). Anal. Calc. for $C_{17}H_{12}ClN$: C, 76.84, H, 4.55, N, 5.27; Found: C, 77.07, H, 4.38, N, 5.09%.

2,3-methylenedioxyl-5,6-dihydrobenz[c]acridine (**4c**): m.p. 206–208˚C. IR: 3050, 2990, 1652, 1618, 1547, 1471, 1377, 1314, 1267, 1200, 1030, 964, 925, 865, 845, 784, 757, 682. ^{1}H NMR: 2.98(2H, t, *J*=7.2Hz, CH_2), 3.08(2H, t, *J*=7.2Hz, CH_2), 6.29(2H, s, OCH_2O), 7.43–7.48(4H, m, ArH), 7.66(1H, s, ArH), 8.33(1H, s, ArH), 8.43(1H, d, *J*=6 Hz, ArH). Anal. Calc. for $C_{18}H_{13}NO_2$: C, 78.53, H, 4.76, N, 5.09; Found: C, 78.73, H, 4.54, N, 5.21%.

2,3-dimethoxyl-5,6-dihydrobenz[c]acridine (**4d**): m.p. 175–176˚C. IR: 3050, 2990, 1621, 1585, 1503, 1453, 1426, 1386, 1320, 1291, 1239, 1145, 1009, 911, 843, 792, 760, 735. ^{1}H NMR: 2.94(2H, t, *J*=7.2Hz, CH_2), 3.04(2H, t, *J*=7.2Hz, CH_2), 3.90(3H, s, OCH_3), 3.94(3H, s, OCH_3), 7.27(1H, s, ArH), 7.31–7.40(4H, m, ArH), 7.98(1H, s, ArH), 8.38(1H, d, *J*=5.6Hz, ArH). Anal. Calc. for $C_{19}H_{17}NO_2$: C, 78.33, H, 5.88, N, 4.81; Found: C, 78.47, H, 5.64, N, 4.75%.

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References

1 J.E. McMurry, *Chem. Rev.*, 1989, **89**, 1513.
2 D. Lenour, *Synthesis*, 1989, 883.
3 D.Q. Shi, Z.S. Lu, L.L. Mu and G.Y. Dai, *Synth. Commun*., 1998, **28**, 1073.
4 L.H. Zhou, S.J. Tu, D.Q. Shi and G.Y. Dai, *J. Chem. Res*., (s), 1998, 398.
5 L.H. Zhou, S.J. Tu, D.Q. Shi, G.Y. Dai and W.X. Chen, *Synthesis*, 1998,
6 D.Q. Shi, J.X. Chen, W.Y. Chai, W.X. Chen and T.Y. Kao *Tetrahedron Lett*., 1993, **34**, 2963.
7 D.Q. Shi, L.L. Mu, Z.S. Lu and G.Y. Dai, *Synth. Commun*., 1997, **27**, 4121.
8 L.H. Zhou, D.Q. Shi, G.Y. Dai and W.X. Chen, *Tetrahedron Lett*., 1997, **38**, 2729.
9 L.S. Huang, *Acta Pharm. Sinica*, 1983, **18**, 553.
10 L.S. Huang, *Acta Pharm. Sinica*, 1983, **18**, 633.
11 Y. Akira, K. Kazuo, *Radioisotopes*, 1979, **28**, 687.
12 P.A. Claret, in *Comprehensive Organic Chemistry*, Vol. 4, pp155; D.H.R. Barton and W.D. Ollis, (eds); Pergamon Press: Oxford, 1979.
13 K. Milton, *J. Nat. Prod*., 1990, **53**, 1508.
14 C.C. Cheng and S.J. Yan, *Organic Reactions*, 1982, **28**, 37.
15 C.E. Castro, E.J. Gaughan and D.C. Owsley, *J. Org. Chem*., 1966, **31**, 4071.
16 D. Nanni, *J. Org. Chem*., 1992, **57**, 1842.
17 R.C. Larock and M.Y. Kuo, *Tetrahedron Lett*., 1991, **32**, 569.
18 N.G. Kundu, J.S. Mahanty, P. Das, B. Das, *Tetrahedron Lett*., 1993, **34**, 1625.
19 C. Boix, J.M. Delafuente, M. Poliakoff, *New. J. Chem*., 1999, **23**, 641.